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Chemical Preparation Laboratory for IND Candidate Compounds

Annual Report

E.M. Schubert, Ph.D.

February 8, 1990

(January 17, 1989 - January 16, 1990)

Supported by

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07	03		
06	03		

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

During the reporting period seven compounds were synthesized and submitted to USAMRIID for testing. Most of these compounds were modified nucleosides derived from ribavirin, selenazole and formycin B, together with triazole heterocycles and an organic ester.

Compounds which remain under investigation are a large-scale preparation of Ribavirin as well as the exploratory synthesis of dimethyl-ribavirin amidine and prodrug ester.

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I. SUMMARY

During the reporting period the synthesis of ten target compounds have been examined, and the preparation of seven had been completed. Two compounds, AVS 253 (Selenazole) and AVS MTE, were synthesized twice and submitted separately.

The following compounds were delivered: Thioformycin B (AVS-57); Methyl-1,2,4-triazole-3-carboxylate (AVS MTE); Selenazole (AVS 253); 1-β-*D*-Ribofuranosyl-1,2,4-triazole-N-methyl-carboximidate hydrochloride (AVS-5058); 4-nitro-3-(octanoyloxy) benzoic acid (AVS OCT).

The preparations of the following target compounds remains under investigation, and their syntheses are progressing: 1-β-*D*-Ribofuranosyl-1,2,4-triazole-N,N-dimethyl carboxamidate hydrochloride (AVS 5601); Ribavirin (AVS-1) and Prodrug ester (AVS XYZ).

II. FOREWORD

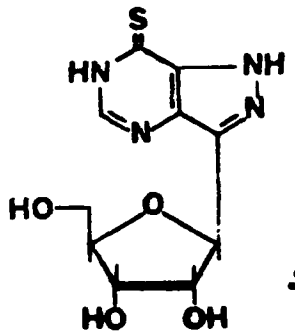
All information in this report is the property of the U.S. Army Medical Research and Development Command. The contractor retains no copyright or patent rights.

All target compounds reported herein were prepared in strict compliance with "Current Good Manufacturing Procedures" (CGMP) guidelines. All intermediates and final products unreported in the chemical literature were fully characterized by elemental and spectral analyses.

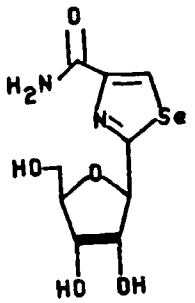
IIIa. CUMULATIVE LIST OF COMPOUNDS COMPLETED AND DELIVERED TO U.S. ARMY MEDICAL RESARCH INSTITUTE OF INFECTIOUS DISEASES (USAMRIID)
JANUARY 17, 1988 TO JANUARY 16, 1989

No.	Compound	Amount	Production Control No.
AVS 52	3-β-D-Ribofuranosyl-1(4)pyrazole [4.3d]pyridine-7(CH) thione (Thioformycin B)	5.85 g	2585
AVS 253	2-β-D-Ribofuranosyl-selenazo-4-carboxamide	37.8 g	2717
AVS MTE	Methyl-1,2,4-triazole-3-carboxylate	5.0 g	
AVS 5058	1-β-D-Ribofuranosyl-1,2,4-triazole-N-methyl-carboximidate hydrochloride	15.1 g	2792
AVS 253	2-β-D-Ribofuranosyl-selenazo-4-carboxamide	50.9 g	2800
AVS OCT	4-nitro-3-(octanoyloxy) benzoic acid	12.0 g	2836
AVS MTE	Methyl-1,2,4-triazole-3-carboxylate	5.0 g	QC4014

IIIb. STRUCTURES OF COMPOUNDS SUBMITTED



AVS 52



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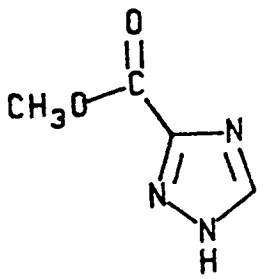
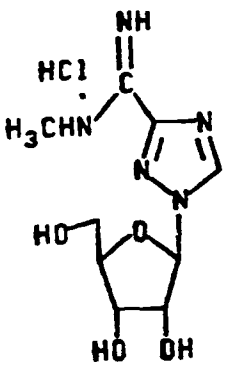
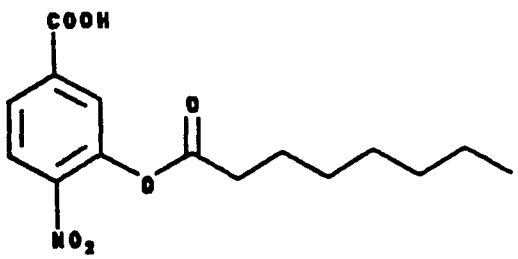
AVS 253



AVS TAE



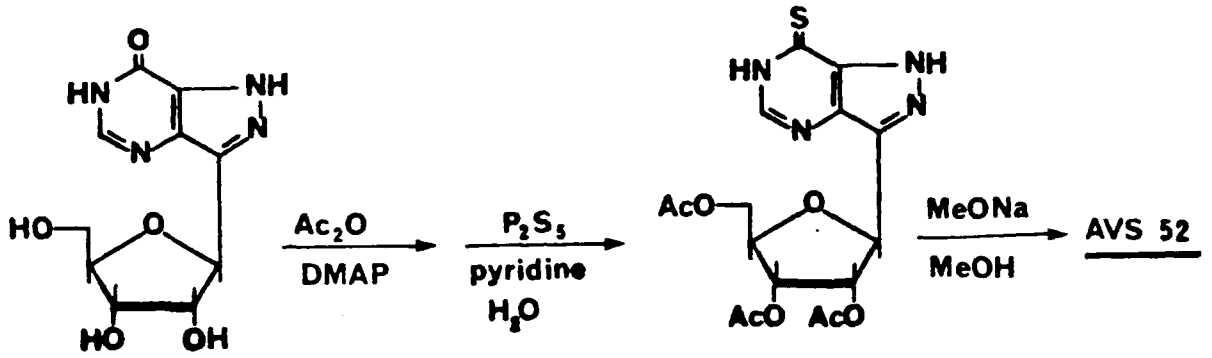
AVS 5058



AVS OCT

IV. **PROCEDURES FOR TARGET COMPOUNDS DELIVERED TO USAMRIID**
from January 17, 1989 to January 16, 1990

AVS-52 was synthesized according to the following scheme:



Experimental

3-(2,3,5-Tri-O-acetyl-ß-D-ribofuranosyl)-1(H)pyrazolo[4,3-d]pyrimidin7(6H)one, (Tri-O-acetylformycin-B): A mixture of Formycin-B (7.95 g, 29.66 mmol), 4-dimethylaminopyridine (200 mg) and acetic anhydride (200 ml) is stirred under anhydrous conditions at room temperature for 48 hours. Acetic anhydride is evaporated under reduced pressure and the residue is coevaporated with ethanol (1 x 100 ml). The syrupy material is refluxed gently for 30 minutes with ethanol-water (80:20, 150 ml) and cooled in an ice bath. The crystalline material is filtered and washed with water. Yield 8.0 g. The mother liquor is concentrated and cooled, the resulting crystalline material is filtered and washed with water to yield 2.0 g. An additional 0.2 g of the product is recovered from the above filtrate. The combined yield is 10.2 g (87.25%); m.p. 168°C (Lit. m.p. 168°C).

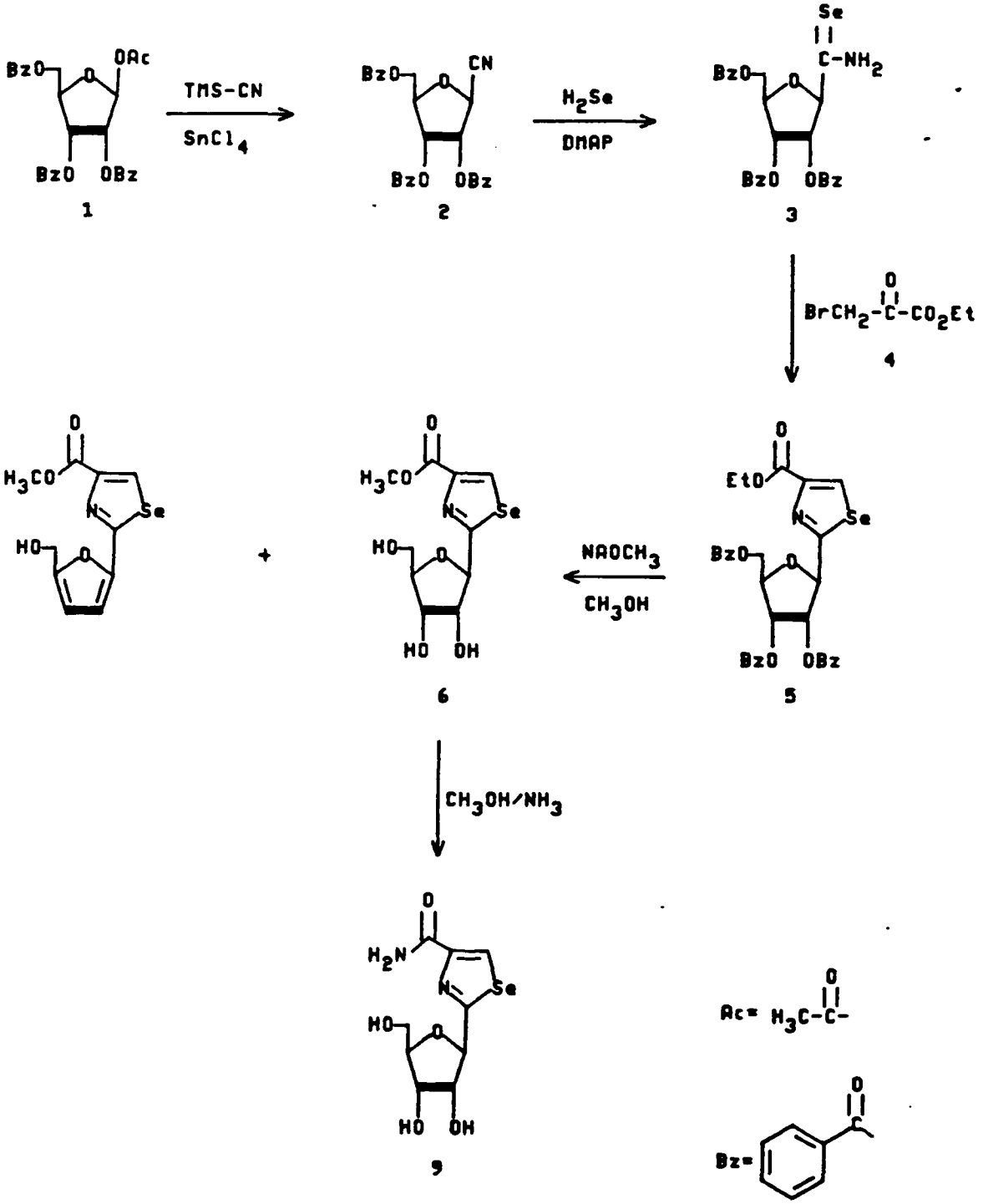
3-(2,3,5-Tri-O-acetyl-ß-D-ribofuranosyl)-1(H)pyrazolo[4,3-d]pyrimidin7(6H)-thione, (Tri-O-acetylthioformycin-B): To a well-stirred mixture of tri-O-acetylformycin-B (10.0 g, 25.4 mmol) and pyridine (350 ml), phosphorus pentasulfide (25 g, 56.0 mmol) is added. Water (3.7 ml, 200 mmol) is added dropwise and the reaction mixture is refluxed for 4.5 hours in an oilbath (bath temp. 135--40°C). The reaction mixture is cooled, chilled in an ice-water bath, and the supernatant liquid is decanted. The residue in the flask is carefully added to boiling water (500 ml). The previously decanted liquid is evaporated to a syrup and added slowly to the above boiling water while stirring. The reaction mixture is cooled and extracted with chloroform (3 x 300 ml). The chloroform layer is washed with saturated sodium chloride solution (2 x 400 ml) and is dried over anhydrous sodium sulfate. Evaporation of the solvent gives a yellow foam. Yield 10.3 g (99%). m.p. 110°C.

3-ß-D-Ribofuranosyl-1(H)pyrazolo[4,3-d]pyrimidin-7(6H)thione, (Thioformycin-B): Tri-O-acetylthioformycin-B (10.0 g, 24.4 mmol) is dissolved in anhydrous methanol

(200 ml) and the pH of the solution is adjusted to ~9-10 by adding sodium methoxide solution. The reaction mixture is stirred at room temperature for 4 hours, neutralized with Amberlite IR-120 H^+ resin and filtered. The resin is washed with methanol (4 x 30 ml) and the filtrate is evaporataed to yield a yellow solid, which is crystallized from methanol-water (9:1). Yield 6.0 g (86%); m.p. 233-234°C (Lit. m.p. 233°C).

Remark: Starting with 9.85 g Formycin-B, an identical second run produced 7.2 g Thioformycin-B. The two batches were combined to give a total yield of 11.0 g of analytically pure Thioformycin-B.

AVS-253 was synthesized according to the following scheme:



AVS 253

Experimental

2,3,5-Tri-O-benzoyl-ß-D-ribofuranosyl-1-carbonitrile (2) : Trimethylsilyl cyanide (200 mL, 1.58 mol) is combined with an ice cold solution of 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribose (531 g, 1.053 mol) in dry methylene chloride (2L). Stannic-IV-chloride (42 mL) is added dropwise to the stirred solution, after 30 min. the ice bath is removed and stirring is continued at room temperature for one hour. The reaction mixture is poured into a saturated sodium bicarbonate solution (2.5L) and stirred vigorously. After filtering through a Celite pad the organic layer is separated and the aqueous layer is washed with methylene chloride (1L). The combined organic layers are dried over sodium sulfate and evaporated under reduced pressure to leave a viscous oil. The oil is loaded on a silica gel column and eluted with methylene chloride. The fractions containing compound 2 are combined and evaporated. The obtained crystalline material is crushed, filtered, washed with little ethanol and dried.

Yield = 380 g (77%) M.P. 75-76° (lit 77-80°)

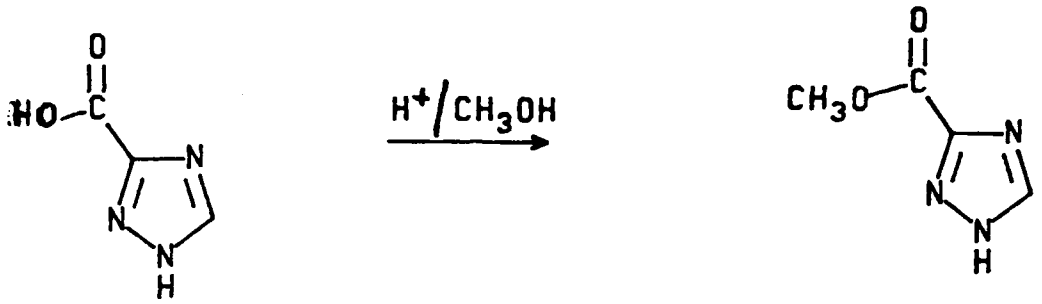
Ethyl-2-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-4-selenazole-carboxylate (5): Dimethylaminopyridine (4.0 g, 0.032 mol) and 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl-carbonitrile (2) (157.5 g, 01.334 mol) are combined with ethanol (2L) and warmed to 40°. The obtained solution is cooled to 20°, the apparatus is purged with argon gas, then hydrogen selenide gas (28 g, 0.346 mol) is slowly bubbled into the solution. Escaping hydrogen selenide gas is deactivated by an attached chlorine bleach trap. After TLC (benzene/ethylacetate 4:1) indicates complete selenium addition the apparatus is again purged with argon gas and ethyl bromopyruvate (4) (49 mL, 0.39 mol) is slowly added to the dark green solution. After stirring for 45 min. and when TLC shows almost complete selenazole formation the red solution is adjusted to pH 7 with saturated sodium bicarbonate solution. The mixture is filtered through a Celite pad and the red precipitate is washed with methylene chloride (1L) and ethanol (1L). The filtrate is evaporated under reduced pressure and the obtained oil is dissolved in methylene chloride (500 mL). The organic layer is washed with sodium bicarbonate solution (400 mL), separated, and the aqueous layer is washed with methylene chloride. The combined organic layers are washed with water twice, dried over sodium sulfate and evaporated under reduced pressure to leave a dark red solid foam, yield 209.2 g (96%). This crude material is used in the next step without further purification.

2-β-D-Ribofuranosylselenazole-4-carboxamide (9): Crude selenazole derivative 5 (209.2 g, 0.33 mol) is dissolved in methanol (710 mL) with slight warming, then sodium methoxide (15.6 g, 0.288 mol) is added and the solution is stirred at room temperature for four hours. After TLC indicates deprotection Amberlite IR-120H+ resins (100 g) in added and stirring is continued for 1 hour. The resin is collected by filtration, washed with methanol and the filtrate is evaporated to dryness under reduced pressure. The residue is dissolved in ethanol, silica gel (100 g) is added and the ethanol is evaporated to leave the product coated on silica gel, which is loaded onto a silica gel column. Elutions of the compound mixture, first with methylene chloride, then with increasing methanol addition to the methylene chloride when fractions are obtained that contain the deblocked selenazole derivative 6. After evaporation of the combined fractions containing 6 46.3 g of a grayish-white powder is obtained.

Compound 6 is dissolved in methanolic ammonia at 0°C (800 mL), placed in a steel bomb and stirred for 24 hours at room temperature. The solution is

evaporated to dryness under reduced pressure, the obtained solid foam is dissolved in hot isopropanol/ethanol, treated with charcoal and filtered. After standing overnight the precipitated white crystals are collected by filtration and dried. Total yield: 39.1 g, M.P. 130° (lit 129-131°).

AVS-TAE was synthesized according to the following scheme:



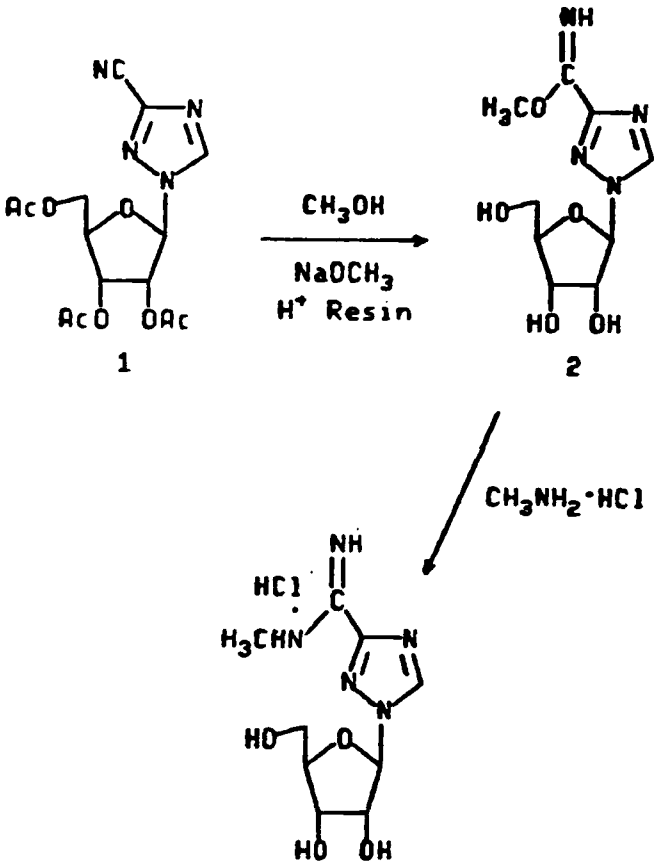
Experimental:

Methyl-1,2,4-triazole-3-carboxylate:

To a suspension of 1,2,4-triazole-3-carboxylic acid (18 g, 0.16 mol) in methanol (120 mL) hydrochloric acid gas is injected while maintaining the temperature below 20° with cooling. After gas saturation the obtained solution is left at room temperature for five days. After that time the precipitated hydrochloride salt is collected by filtration, and dried, then added to water (400 L) for hydrolysis. The methyl ester is filtered and dried. The crude material, obtained from several batches , is recrystallized from boiling water (250 mL) to give purified crystalline methyl-1,2,4-triazole-3-carboxylate.

Total Yield: 2560 g m.p. 198-199° (lit. 198°)

AVS-5058 was synthesized according to the following scheme:



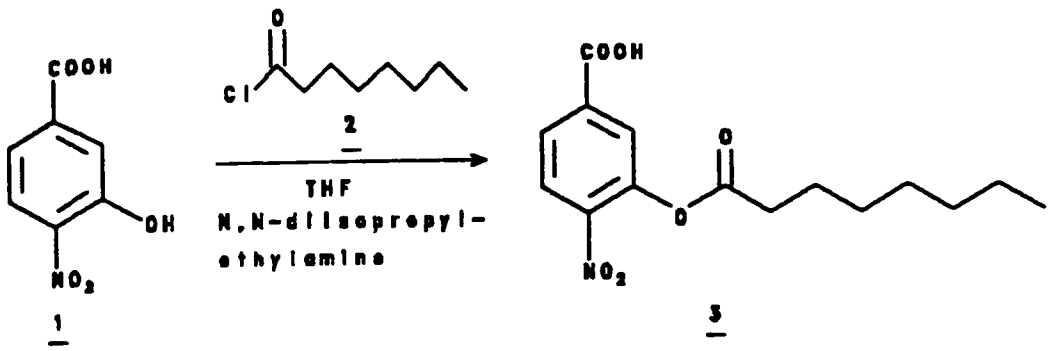
Experimental:

Methyl-1-(*B*-D-ribofuranosyl)-1,2,4-thiazole-carboximidate (2) Carbonitrile 1 (40 g, 0.11 mol) is dissolved in methanol (930 mL), sodium methoxide (0.96 g) is added and the resulting solutions with pH 8.5 is stirred for 4-1/2 hours. The reaction rate is monitored by TLC (silica gel, dichloromethane - methanol 6:1) and upon completion Amberlite H^+ resin (5 g) is added. Upon showing pH 6 the Amberlite is filtered off, and the filtrate is concentrated under reduced pressure until crude carboximidate (2) forms as a yellowish solid foam (25.68 g) which is recrystallized from methanol (300 mL) to give 2 as a white, crystalline material, yield 22.21 g (76%), m.p. 139-141°.

N-methyl-ribavirin amidine-hydrochloride (3): Carboxamidate 2 (20.0 g, 77.45 mmol) is combined with methylamine hydrochloride (5.23 g, 77.45 mmol) followed by the addition of methanol (400 mL). The mixture is stirred and heating gently until TLC monitoring (dichloromethane-methanol ^:1) indicates the completion of the reaction. The solvent is evaporated under reduced pressure, the obtained solid foam is dissolved in ethanol (150 mL), again concentrated under reduced pressure until it leaves a semi-solid product which, upon trituration with ether-ethanol 4:1 (500 mL) affords N-methyl amidine 3; yield 20.26 g (89%) m.p. 175-177°.

AVS OCT

Experimental

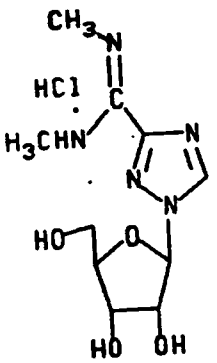


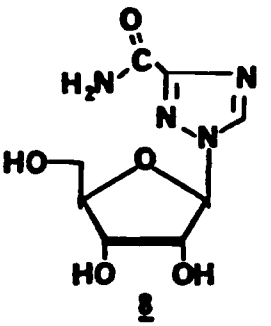
Octanoyl chloride (16.3 g, 0.1 mol) is dissolved in dry tetrahydrofuran (1 L) and maintained under a dry argon atmosphere. The solution is cooled to 0° and a suspension of 3-hydroxy-4-nitrobenzoic acid (18.3 g, 0.1 mol) and diisopropyl-ethylamine (25.9 g, 0.2 mol) in dry tetrahydrofuran (600 mL) is added dropwise. After completion of addition the reaction mixture is allowed to warm up to room temperature while stirring is continued overnight. Subsequently the reaction mixture is warmed gently to dissolve all the remaining solids, after cooling again the mixture is filtered, and the solid residue is washed with ether (3 X 200 mL). The combined organic filtrates are evaporated to dryness under reduced pressure, the residue is dissolved in ether-hexane 2:1 (2 L), washed with 0.1 N hydrochloric acid (2 X 200 mL) and with deionized water (2 X 200 mL) and dried over sodium sulfate. After evaporating the solvent under reduced pressure a yellowish-white solid is obtained and it is purified on a silica gel column with hexane-ethyl ether-acetic acid 1:1:0.1 as the eluant. The fractions containing the octanoyl ester 3 (Rf 0.65) are pooled, the solvent is evaporated under reduced pressure and the residue is recrystallized from hexane-ethylacetate 5:1 to yield pure title compound 3 as an off-white, amorphous solid.

Yield: 12.8 g (41%) M.P. 144-145°
lit. 142-143°

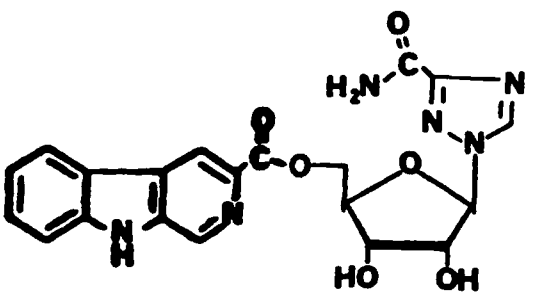
V. Discussion of uncompleted Target Compounds

List and Structures of Compounds in Progress

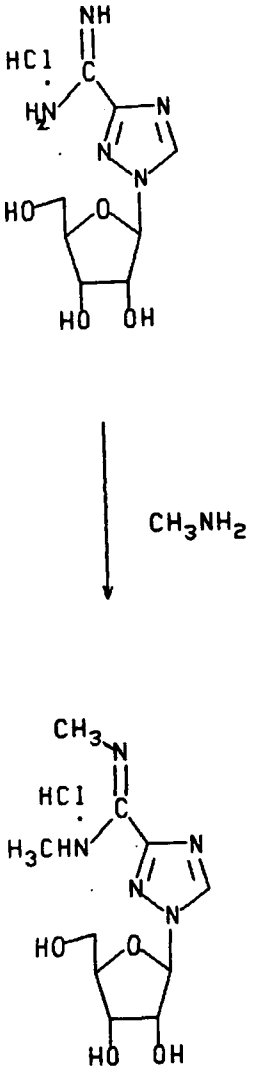




AVS-Rib
(Ribavirin)

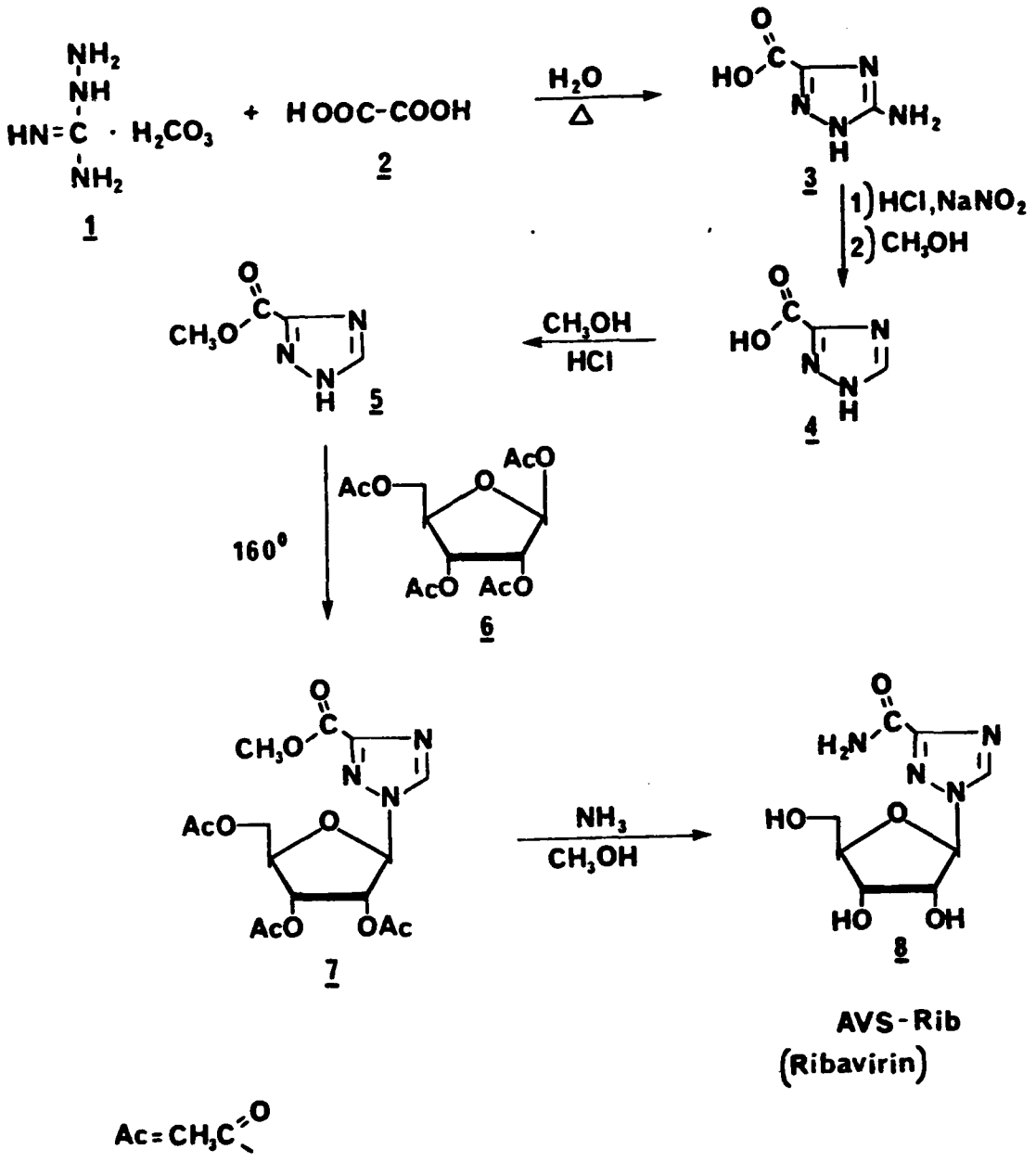


The preparation of AVS 5601 was attempted according to the following scheme:

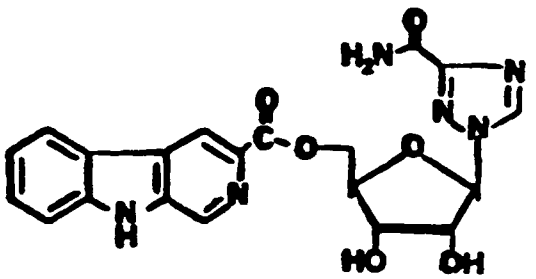


The reaction, performed at atmospheric pressure, did not produce any separable amount of product, therefore reactions under increased pressure are presently being studied to allow for its synthesis.

The preparation of 1 Kg of Ribavirin (AVS 1) is presently in progress, according to the following scheme. Sufficient amounts of heterobase have been prepared to enable the completion of the assignment.



AVS-XYZ



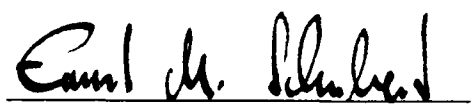
Presently the coupling of β-carbinole with ribovirin is still being investigated, where is appears that the intended reaction resists all the known coupling procedures. Still more experimental work is being performed as time allows.

The contract expired January 15, 1990 and no additional compound had been assigned. An extension granted until May 31, 1990 enables the completion of the compounds in progress under a two-man work effort.

VI. ACKNOWLEDGMENTS

The personnel assigned to this contract during the past annual period were: Ernst M. Schubert, Ph.D., Principal Investigator; Krishna Upadhya, Ph.D., Principal Assistant, and Gary Era, B.S., Chemist.

Report Submitted By:
Pharm-Eco Laboratories, Inc.



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VIII. APPENDIX

Reprint of Publication

PREPARATION AND ANTIVIRAL ACTIVITY OF SEVERAL DEOXYGENATED RIBAVIRIN AND TIAZOFURIN DERIVATIVES.

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Gwendolyn N. Chmurny, Program Resources Inc. NCI-FCRF, P.O. Box B, Frederick, MD 21701, and Bjarne Gabrielsen, US Army Medical Research Institute of Infectious Diseases, Fort Detrick, Frederick, MD 21701-5011.

Abstract: Ribavirin and tiazofurin, two nucleosides of known antiviral activity, have been transformed by previously reported methods to yield several deoxy,epoxy, or dideoxy analogues. The deoxygenated derivatives were evaluated for antiviral activity against a host of DNA and RNA viruses; however, no significant *in vitro* activity was detected.

In the past, a number of 2'3'-dideoxynucleosides have been prepared and evaluated for their antiviral activity. Such studies were mostly directed towards suppressing the replication of the human immunodeficiency virus in the treatment of the acquired immune deficiency syndrome (AIDS). 3'-Azido-3'deoxy-thymidine (AZT)[1] and 2'3'-dideoxycytidine (ddCyd)[2] were found to be the most active pyrimidine nucleosides, while recent studies indicate that 2'3'-dideoxyinosine (DDI), a purine riboside derivative, might find wide clinical application in the treatment of AIDS.[3]

Since none of the parent nucleosides such as thymidine, cytidine, or inosine show any noticeable antiviral activity, it was thought that the transformation of a ribonucleosides of known antiviral activity such as ribavirin or tiazofurin[5] into their deoxygenated derivatives would offer the possibility of augmenting their respective biological activities, or enhancing their therapeutic specificity. Analogously, a recent publication by Krawczyk and Townsend[6] reports the synthesis of the 2'3'-dideoxy derivatives of the antibiotics tubercidin, toyocamycin and sangivamycin as examples of biologically active purine nucleosides which were transformed into agents that might demonstrate anti-HIV activity.

Since the preparation of 2',3'-dideoxyribosides as well as those of other sugar-modified nucleosides has been the topic of a number of studies in recent

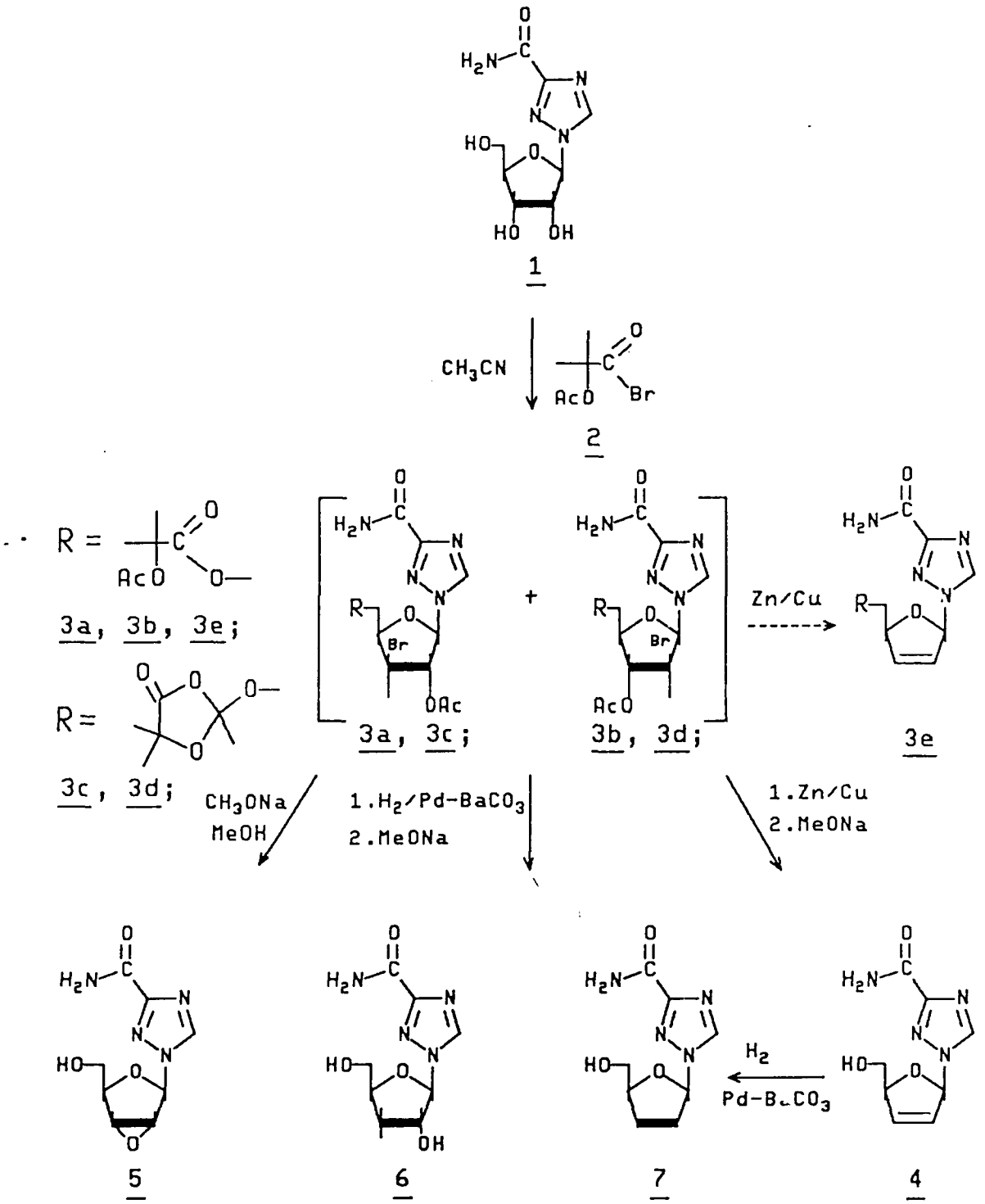
years, there are several methodologies, such as the modified Corey-Winter reaction[7] and other elimination[8] or synthesis methods[9] available to accomplish such transformations. During the course of this study we found that a modified procedure, based on work reported by Robins et al.[10] was best suited for transforming both the N-nucleoside ribavirin and the C-nucleoside tiazofurin into various sugar-modified analogues via a common intermediate (3a-d and 9a-d) by essentially using identical reagents and reaction conditions.

Both ribavirin (1) and tiazofurin (9) were acylated with α-acetoxy-isobutyryl bromide (2), as shown in Schemes 1 and 2, to form a mixture of four possible intermediates, shown by structures 3a-d and 9a-d. This mixture of intermediate isomers was subjected to transformations without further characterization; however, upon careful dehydrohalogenation and purification of either 3a-d or 9a-d without deblocking the 5'-position, the ^{1}H NMR spectrum of the purified product 3e or 9e showed the two α-methyl groups of the side chains as one singlet (6H), indicating the existence of the open chain, and not the sterically rigid dioxolone ring configuration as a possible structure.

The treatment of 3 and 9 with zinc/copper couple and sodium methoxide readily yielded *enes* 4 and 10 respectively, which in turn were readily hydrogenated to form 2'3'-dideoxyribavirin (7) and 2'3'-dideoxytiazofurin (11) in good yield.

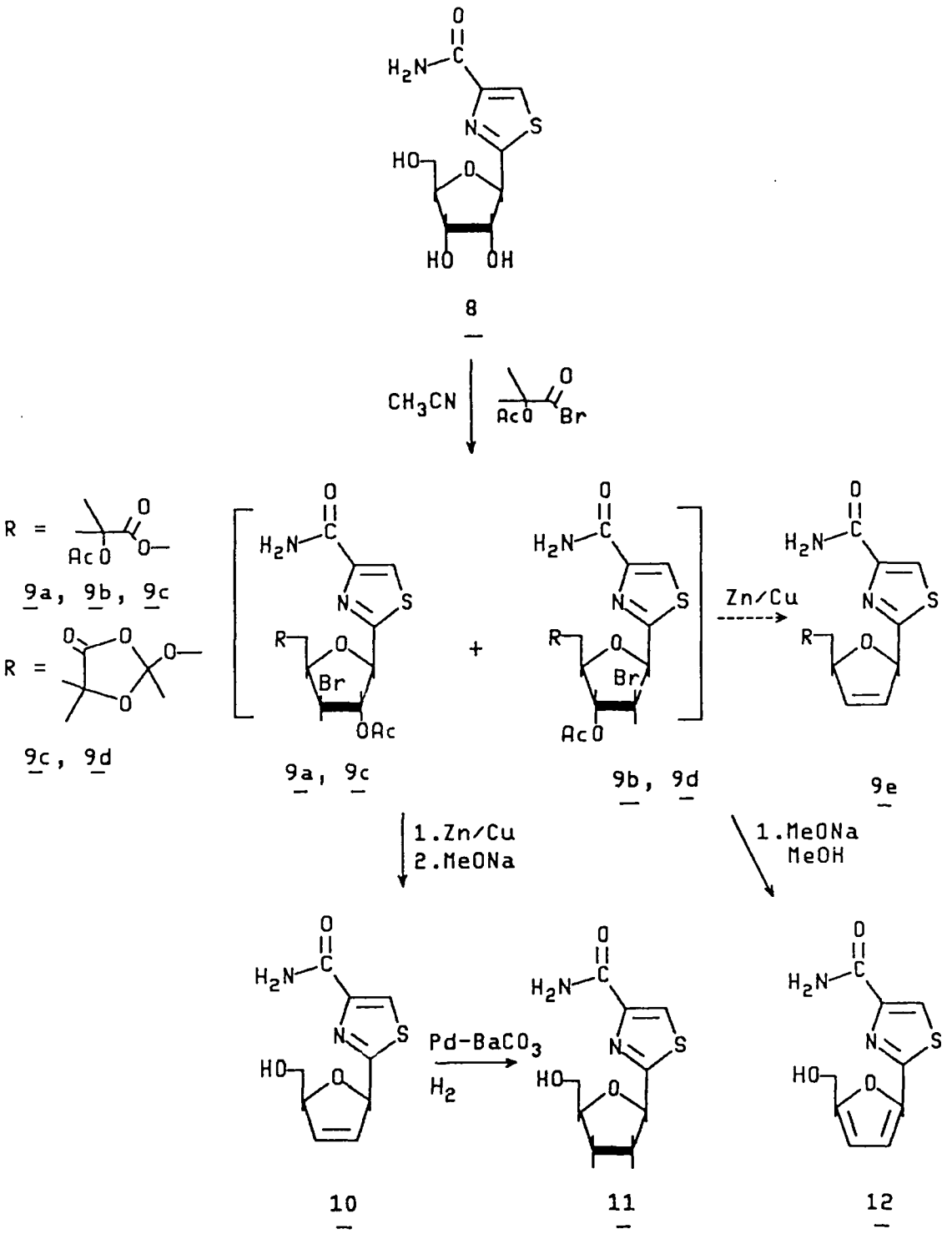
Hydrogenation of 3, followed by deblocking, gave 2'3'-dideoyxribavirin (7). The major product isolated from this reaction, however, was 3'-deoxyribavirin (6), as identified by comparison with data published by Witkowski et al. The treatment of 3 with sodium methoxide in methanol produced 2',3'-anhydroribavirin 5; yet, when the same reaction conditions were applied to 9, it resulted in double elimination and formation of the furan derivative of the thiazole amide 12, first reported by Srivastava et al.[5]

2'3'-Dideoxyribavirin, previously prepared by a different route and shown to be inactive against the HIV virus[12] was still considered a viable candidate to be screened as part of the whole series of obtained compounds against a number of different RNA and DNA viruses, as discussed below.



Ribavirin Series

SCHEME 1



Tiazofurin Series

SCHEME 2

Ribavirin (1) possesses considerable activity in vitro against RNA viruses of the Bunyaviridae family[13,14] (Rift Valley fever, RVF'sandfly fever, SFS, and Punta Toro, PT viruses).[15] Activity has also been demonstrated against the retrovirus human immunodeficiency virus type 1 (HIV-1)[16], the DNA-containing adenovirus type 2 (AD2)[13], and vaccinia virus (VV),[13] and the RNA-containing alphavirus, Venezuelan equine encephalomyelitis virus (VEE)[13,14]. Activity is also present, but to a lesser degree, against RNA viruses of the Flaviviridae family, yellow fever (YF), and Japanese encephalitis (JE) viruses[13,14]. Virtually no activity is observed against vesicular stomatitis virus, VSV (Rhabdoviridae family)[13]. Tiazofurin **8**, possesses some activity in vitro against the flaviviruses YF and JE[13,14], lesser activity against the bunyaviruses RVF, PT[13,14] and SFS, and the DNA-containing adenovirus and vaccinia virus[13]. No activity has been reported against HIV, VEE, and VSV[13].

In vitro antiviral activities were determined for the deoxygenated ribavirin analogues **4-7** and tiazofurin analogues **10-12** against human immunodeficiency virus (HIV-1), the RNA-containing bunyaviruses (Rift Valley fever, sandfly fever, and Punta Toro viruses), flaviviruses (Japanese encephalitis and yellow fever viruses), alphavirus (Venezuelan equine encephalomyelitis virus), rhabdovirus (vesicular stomatitis virus), and the DNA-containing adenovirus type 2 and vaccinia virus. The observed antiviral activities are summarized in the accompanying table. Replacement of the ribofuranosyl group in the deoxygenated tiazofurin analogues **10-12** resulted in the loss of all in vitro antiviral activity previously observed for tiazofurin **8** against the flaviviruses, bunyaviruses and DNA viruses, and vaccinia and adenovirus type 2. Compounds **10-12** were also inactive against HIV-1, VEE, and VSV.

Replacement of the ribofuranosyl group of ribavirin 1 by 2',3'-dideoxy (**7**), 3'-deoxy (**6**), or 2',3'-anhydro (**5**) ribofuranosyl moieties resulted in elimination of all antiviral efficacy against HIV-1, vaccinia and adenoviruses, flaviviruses (JE, YF), Venezuelan equine encephalomyelitis (VEE), bunyaviruses (PT, SFS) and no resulting activity against vesicular stomatitis virus (VSV).

2',3'-Dideoxy-2',3'-didehydro ribavirin 4 retained some efficacy only against the bunyaviruses (RVF, PT, SFS) and vaccinia virus, however the level of efficacy in vitro was greatly reduced compared to that of ribavirin. Similar reduced activity was also observed against Rift Valley fever virus by 5-7. Plaque reductions of 80% (@ 100 ug/mL), 59%, 76% and 94% were observed for 4-7 respectively against RVF virus in Vero cells at 250 ug/mL. However the activities of 4-7 against RVF could not be separated from the accompanying Vero cell toxicity. 2',3'-Dideoxyribavirin 7 and 3'-deoxyribavirin 6 were evaluated further in the murine model of Rift Valley fever virus[17]. Doses of 25, 125 and 250 mg/kg/day were administered subcutaneously in 10% DMSO-PBS or saline on days -1 to +3. No beneficial effects were observed in terms of increased survival numbers or times, nor were the compounds toxic at these doses (virus ratings, VR, 0.96-0.99). As a positive control, ribivirin at doses of 100 and 200 mg/kg/day protected 100 % of the RVF-infected mice (VR = 5.4 and 6.1 respectively).

IN VITRO ANTIVIRAL TESTING DATA[e]

Compound	Virus	ID_{50}[a]	MTC[b]	TI[c]	[d]TI[+]
4	RVF	61	<100	1.6	6.6
4	SFS	5	10	2.0	5.6
4	PT	28	32	1.1	6.3
4	YF	73	10	0.1	1.2
4	VV	36	100	2.8	7.5
5	RVF	149	250	1.7	6.6
6	RVF	117	250	2.1	6.6
7	RVF	101	<250	2.5	6.6

[a] 50% Viral Inhibitory dose, µg/ml
[b] Minimum Toxic Concentration, µg/ml
[c] Therapeutic Index, TI = MTC_{50}/ID_{50}
[d] Positive drug controls : ribavirin (RVF, SFS, PT), selenazofurin (YF, JE), adenosine arabinoside, ara-A (VV)
[e] Vero cells

EXPERIMENTAL SECTION

Analytically pure ribavirin and tiazofurin were provided by US Army Medical Research Institute for Infectious Diseases, Ft. Detrick, MD.

Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. The utilized Zn/Cu couple contained 5% copper. Silica gel used for chromatography was flash grade (Aldrich, 260-400 mesh), and thin-layer chromatography (TLC) was performed on prescored silica gel plates GHLF, 250 microns (Analtech Corp., Newark, DE.) with 6:1 dichloromethane-methanol as developing solvent. TLC plates were sprayed with 10% methanolic sulfuric acid after elution and heated to visualize the compounds. IR spectra were recorded using a Beckman AccuLab 2 spectrophotometer, and elemental analyses were performed by MHW Laboratories, Phoenix, Arizona.

All of the NMR spectra with the exception of **12** were obtained on a Varian VXR500S NMR spectrometer equipped with a SUN 4/110 acquisition computer and data station. The following 90° pulse widths were used for 1D and 2D data acquisition: proton, observe = 14.0 μsec, Waltz decouple = 89.3 μsec; carbon, observe = 15.0 μsec, Waltz decouple = 30.8 μsec, 2D 90° PW = 29 μsec. For 1D experiments, the Ernst angle was used for acquisition. Heteronuclear multiple quantum coherence (hmqc) standard pulse sequence from Varian software was used to obtain directly bonded, indirectly detected proton-carbon connectivities (ref. Bax, $^{1}J_{CH}$ = 150 Hz)[18]. Heteronuclear multiple bond connectivity (hmbc) was modified from Varian software according to Bax[18] and used to detect long range proton-carbon connectivities (Jnxh - 8 Hz). Standard Varian COSY was used for proton-proton connectivity determination. Zero field decoupling (ZFD) and modified Varian software were used to obtain chemical shift and coupling information.

Spectra of **12** were obtained on a Varian XL200 with an ADVANCE data system operating at 200.1 MHz. The following 90° pulse widths were operational: proton,observe = 23.5 μsec, Waltz decoupling = 79.2 μsec; carbon, observe = 9 μsec. The Ernst angle was used for 1D data acquisition.

Definition of J coupling notations: capital letters in ^{13}C coupling

patterns refer to directly bonded $^1J_{C-H}$ while lower case letters refer to J coupling over more than one bond. For example, Ddt (156, 2.0, 10.8) means that the carbon in question has a directly bonded J_{CH} of 156 Hz, a long-range coupling to one proton of J = 2.0 Hz and a long range coupling to two protons of J = 10.8 Hz, s = singlet, d = doublet, t = triplet, q = quartet, b = broad, cm = complex multiplet.

The chemical shifts in the proton spectra are referenced from tetramethylsilane (TMS) set equal to 0 ppm. The chemical shifts in the carbon spectra are referenced with respect to dimethylsulfoxide-d_6 ($DMSOd_6$) set equal to 39.5 ppm from TMS.

In vitro antiviral activity was determined in terms of therapeutic index by observing inhibition of viral cytopathic effect (CPE)[13,15,19-22] except for RVF virus which was determined by plaque reduction assays [14]. The 50% inhibitory dose is that drug dose causing a 50% inhibition of CPE or plaque number. The minimum cytotoxic concentration (MTC) is that drug concentration at which 50% of the cells showed cytotoxic effects. The in vitro therapeutic index (TI, proportional to in vitro activity) was calculated by dividing the MTC by the ID50. Compounds were evaluated for therapeutic efficacy in Rift Valley fever-infected mice according to the procedure of Peters et al[17].The in vivo virus rating, VR, was calculated by dividing the geometric mean time to death of drug-treated, infected animals by that for untreated, infected animals.

1-(2,3-Dideoxy-ß-*D*-glycero-pent-2-enofuranosyl)-1,2,4-triazole-3-carboxamide (4). (2',3'-Dideoxy-2',3'-didehydroribavirin):

Ribavirin (1) (19.5 g, 80 mmol) was dissolved in acetonitrile (200 mL) containing water (1.44 mL, 80 mmol). To this solution was added α-acetoxyisobutyryl bromide (2) (49.4 g, 36 mL, 240 mmol) in one portion, and stirring was continued at room temperature for two hours. After adding 5% sodium bicarbonate solution (200 mL) the mixture was extracted with ethyl acetate (2 x 200 mL), and the organic phase was washed with sodium bicarbonate solution and with brine. After evaporation of the solvent under reduced pressure a highly

viscous foam was obtained, which was dissolved in tetrahydrofuran (600 mL). Zinc/copper couple (80 g) was added, followed by ammonium chloride (50 g) and the reaction mixture was stirred for two hours when the temperature reaches 40°. The zinc/copper couple was filtered off, washed with ethyl acetate and the organic layer was washed with a 5% aqueous solution of ethylenediamine tetraacetic acid tri-sodium salt, followed by washings with bicarbonate (100 mL) and brine (200 mL).

The solvent was removed under reduced pressure, the residue was dissolved in methanol (200 mL) and sodium methoxide (0.5 g) was added to adjust the pH to 9.5. After stirring for three hours a solid started to precipitate. The solvent volume was reduced to half its volume, the precipitate was collected by filtration and recrystallized from methanol-ethyl acetate.

Yield 7.0 g (42%); **m.p.** 152-153°; **IR** (KBr): 3400-3050; 1750; 1480; 1750; 1480; 1270; 1190; 1070; 840; 780 cm^{-1}. **^{1}H-NMR**: (DMSO-d_6) δ 8.75(s, 1, $C_5\underline{H}$); 7.82 and 7.63 (each singlets, 1H each, NH); 6.85(td,1,H-1',J(1',2') = 1.6 Hz, J(1',4') = 2.4 Hz); 6.51 (td, 1,[a]H-3',J(3',4') = 1.7 Hz, J(3',2')=6.1 Hz); 6.13 (ddd, 1,[a1]H-2',J(2',1') = 1.5 Hz, J(2',4) = 2.3 Hz, J(2',3') = 6.0 Hz); 4.914 (ddddd, 1, H-4', J(4',1') = 2.4 Hz, J(4',3') = 1.7 Hz, J(4',2') = 2.3 Hz, J(4,5'a,b) = 4.2, 4.8 Hz, 4.908 (4, 1, 5'-OH, J(OH-5' = 5.6 Hz; 3.48, 3.55 (AB of ABXY, 2, H-5'a,b,J(gem) = 11.6, 11.7, J(5',a,b,4')=4.2, 4.8Hz, J(4', OH) = 5.6 Hz);

^{13}C-NMR: (DMSO-d^6): δ 160.32 (Sq, C=O, J = 1.2 Hz); 156.75 (Sdd, C-3, J = 8.5, 11.7 Hz); 144.13 (Dd, C-5, J = 214.7, 2.7 Hz); 134.58 (Dtdd, C-3', J = 172.3, 4.0, 2.4, 7.4 Hz); 124.56 (Dtd, C-2', J = 176.9, 4.1, 2.5 Hz); 93.24 (Dtd, C-1', J = 171.1, 10.6, 3.6 Hz); 88.61 (Dddt, C-4', J = 149.8, 8.8, 11.3, 2.2 Hz); 62.84 (T, C-5', J = 141.0 Hz);

TLC: R_f 0.7. **Anal.** Calcd. for $C_8H_{10}N_4O_3$: C, 45.61; H, 4.79; N, 26.66;. Found: C, 45.85; H, 4.76; N, 26.85.

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[1]Assigned from coupled ^{13}C spectrum through HMQC.

1-(2,3-Dideoxy-ß-D-glycero-pentofuranosyl)-1,2,4-triazole-3-carboxamide (7) (2',3'-Dideoxyribavirin):

Ribavirin-2'-ene (4) (2.3 g, 11 mmol) was dissolved in methanol (100 mL), and palladium on barium carbonate (500 mg) was added. The mixture was hydrogenated at room temperature and atmospheric pressure for 3 hours. The catalyst was filtered off on a sintered glass funnel, the filtrate was evaporated to dryness under reduced pressure, and the residue was recrystallized from methanol (50 mL) to yield 1.8 g (77%) of dideoxyribavirin, m.p. 153-154°.(lit[12] 154°C) IR (nujol): 3000-2800 (br); 1690; 1460; 1370 cm^{-1}.

^1H NMR:[12] (DMSO d_6) 12: δ 8.81 (s, 1, C_5H); 7.79, 7.59 (each singlet, 1, NH); 6.16 (dd, 1, H-1', J(1'-2'a,b) = 2.6, 6.5 Hz); 4.88 (t, 1, 5'-OH, J = 5.6 Hz); 4.15 (dddd, 1, H-4', J = 5.2, 4.5, 6.0, 9.2 Hz); 3.56 (ddd, 1, H-5'a, J = 11.7, 4.2, 5.7 Hz); 3.47 (dt, 1, H-5'b, J = 11.7, 5.3 Hz); 2.38 (cm, 2, H-2'a,b); 1.98 (cm, 2, H-3'a,b).

^{13}C-NMR: (DMSO d_6): δ 160.37 (S, C=O); 156.84 (Sdd, C-3, J = 8.2, 11.4 Hz); 143.88 (Dd, C-5, J = 214.2, 1.8 Hz); 88.61 (Dcm, C-1', J_{ch} = 170.1 Hz); 82.84 (Dcm, C-4', J_{ch} = 146.3 Hz); 62.86 (Td, C-5', J = 139.8, 4.7 Hz); 31.90 (Tt, C-3', J = 134.1, 3.1 Hz); 25.32 (Tcm, C-2', J_{ch} = 133.0 Hz).

TLC: Rf 0.65. Anal. Calcd. for $C_8H_{12}N_4O_8$: C, 45.27; H, 5.70; N, 26.40. Found: C, 45.26; H, 5.72; N, 26.36.

3'-Deoxyribavirin (6):

Ribavirin (1) (4.88 g, 20 mmol) was dissolved in acetonitrile (60 mL) and α-acetoxyisobutyryl bromide (2) (9 mL, 50 mmol) was introduced in one portion. The reaction mixture was stirred for two hours at room temperature, then ethyl acetate (300 mL) was added to the clear solution. The organic layer was washed with 5% sodium bicarbonate solution (2 x 50 mL), the bicarbonate phase was washed with ethyl acetate (100 mL), and the combined organic phase was washed with water (2 x 50 mL) and saturated brine (50 mL). The ethyl acetate solution was dried over sodium sulfate, and the solvent was evaporated under reduced pressure to yield 9.2 g of (3) as a viscous oil.

The crude material was dissolved in dry methanol (200 mL), then triethylamine (3 mL) was added, followed by 5% palladium on barium carbonate (2 g). The reaction mixture was hydrogenated at room temperature and atmospheric pressure for two hours, then stirring was continued for four more hours. The catalyst was filtered off, the solvent was removed under reduced pressure and the residue was vacuum-dried. After dissolving the residue in methanol (200 mL) sodium methoxide (1.5 g) was added, and after two hours TLC indicated the completion of deblocking, showing the presence of two products: the spot at R_f 0.7 indicated dideoxy-didehydro-ribavirin (4) while the major product at R_f 0.3 represented 3'-deoxy-ribavirin (6).

The solvent was evaporated under reduced pressure, the residue was loaded onto a silica gel column and eluted with methylene chloride, gradually increasing its polarity by adding methanol. Collecting the fractions containing the two compounds, 0.5 g of dideoxy-didehydro-ribavirin (4) and 2.1 g (47%) of 3'-deoxy-ribavirin (6) was obtained, m.p. 141-142°.(lit[11] 141-142°).

IR (nujol): 3400-3000 (br); 2950; 1680; 1600; 1455; 1300; 1110; 1080; 710 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ 8.87 (d, 1, C_5H, $^4J(5,1') = 0.2$ Hz); 7.85 (bs, 1, NH); 7.64 (bs, 1, NH); 5.86 (d, 1, H-1', $J(1'-C_5H) = 0.7$ Hz); 5.74 (bd, 1, 2'-OH, J = 3.8 Hz); 4.98 (bs, 1, 5'-OH); 4.47 (cm, 1, H-4'); 4.43 (bdt, 1, H-2', J(2'-OH) = 5 Hz, $J(2',3') = 9.8$ Hz); 3.65 and 3.52 (both dd, 1 each, H-$5'_{a,b}$, $J(5'^a,5'_b) = 11.7$ Hz, $J(5',4') = 2.4, 4.5$ Hz); 2.12 and 1.90 (both ddd, 1 each, H-$3'_{a,b}$, J(gem) = 13.2 Hz, J(3', 2') = 10.1 Hz, J(3',4') = 1.5, 5.1 Hz.

^{13}C-NMR (DMSO-d_6): δ 160.59 (cm, C=O); 157.26 (Sdd, C-3, $^3J = 8.5, 11.6$ Hz); 144.27 (Dd, C-5, J = 215.6, 2.0 Hz); 94.67 (Dcm, C-1', $^1J_{CH} = 170.3$ Hz); 82.37 (cm, C-41, $1J_{CH} = 148.9$ H_3); 75.50 (Dcm, C-2', $J_{CH} = 153.2$ Hz); 62.59 (Td, C-5', J = 140.2, 3.7 Hz); 33.77 (Tcm, C-3', $J_{CH} = 132.3$ Hz).

TLC: Rf 0.3. Anal. Calcd. for $C_8H_{12}N_4O_4$: C, 42.10; H, 5.30; N, 24.55. Found: C, 42.22; H, 5.41; N, 24.35.

1-(2',3'-Anhydro-ß-*D*-ribofuranosyl)-1,2,4-triazole-3-carboxamide (5)

Ribavirin (1) (2.44 g, 10 mmol) was dissolved in acetonitrile (30 mL) containing water (0.18 mL). While stirring α-acetoxyisobutyryl bromide (2) (4.5 mL, 30 mmol) was added in one portion. After 2 h at room temperature ethyl acetate (200 mL) was added, the solution was washed with sodium bicarbonate solution 5% (2 x 50 mL), the bicarbonate solution was extracted with ethyl acetate (100 mL) and the combined ethyl acetate extracts were washed with water (2 x 50 mL) and saturated brine solution.

The organic phase was dried over sodium sulfate, filtered, and, upon evaporation of the solvent, 5 g of crude material was obtained. The crude product (5 g) was dissolved in 1 M methanolic sodium methoxide solution (40 mL) and stirred for two hours, during which time a solid separated from solution. The solid was collected by filtration and recrystallized from water to yield 1.8 g (80%) of final product, m.p. 233-235°. IR (nujol): 3430; 3265; 3000-2800 (br); 1690; 1600; 1460; 1375; 1290; 1190; 1070; 1030; 970; 860; 830 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ 8.847 (s, 1, C_5H , ^4J < 0.4 Hz if present); 7.879 (s, 1, NH); 7.705 (s, 1, NH); 6.281 (s, 1, H-1', J < 0.7 Hz if present); 4.985 (t, 1, 5'-OH, J = 5.5 Hz); 4.30 (dd, 1, H-2', ^3J(2',1') = 0.5 Hz, J(2',3') = 2.7 Hz); 4.21 (d, 1, H-3', J (3',2') = 2.7 Hz, coupling was small to H-4' if present); 4.18 (dd, 1, H-4', J(4',5'$_{a,b,}$) = 5.8, 6.8 Hz); 3.63 (ddd, 1, H-5'$_a$) and 3.47 (ddd, 1, H-5'$_b$), J(5'$_a$,5'$_b$) = 11.4, 11.3 Hz, J(5'$_{a,b,}$ OH) = 5.6, 5.7 Hz, J(5'$_{a,b,}$4') = 6.8, 5.6 Hz.

^{13}C-NMR (DMSO-d^6): δ 160.11 (Sdd, C=O, ^2J(C-N-H) = 1.1, 2.2 Hz; 157.45 (Sdd, C-3, ^3J = 8.8, 11.5 Hz); 145.56 (Dd, C-5, J = 215.7, 1.6 Hz); 85.26 (Ddd, C-1', J = 171.6, 5.9, 10.6 Hz); 81.21 (Ddcm, C-4', J = 151.9, 11.7, complex multiplet); 60.52 (Tcm, C-5', J = 142.1, complex multiplet); 57.43 (D of pentuplets (to H-5'$_{a,b,}$ H-4' and H-2') C-3', J -193.4, 4.6 Hz); 57.16 (Dt, C-2', J = 197.8, 4.0 Hz).

TLC: Rf 0.32. Anal. Calcd. for $C_8H_{10}N_4O_4$: C, 42.47; H, 4.45; N, 24.77. Found: C, 42.46; H, 4.51; N, 24.88.

2-(2,3-Dideoxy-ß-*D*-glycero-pent-2-enofuranosyl)-thiazole-4-carboxamide (10) (2',3'-dideoxy-2',3'-didehydrotiazofurin):

Tiazofurin (8) (5.12 g, 20 mmol) was suspended in acetonitrile (60 mL) containing water (0.36 mL), and α-acetoxyisobutyryl (2) bromide (9 mL, 60 mmol) was added in one portion. After stirring at room temperature for three hours ethyl acetate (200 mL) was added, and the solution was washed with 5% sodium bicarbonate (2 x 50 mL). The aqueous layer was extracted with ethyl acetate (100 mL), the combined organic layers were washed with water (2 x 50 mL) and brine (50 mL), followed by drying over sodium sulfate.

The solvent was evaporated under reduced pressure and the thus obtained foam was dissolved in tetrahydrofuran (200 mL). Zinc-copper couple (25 g) and ammonium chloride (12 g) were added and the mixture, initially at 40°C, were stirred while allowing the temperature to adjust to room temperature. After 2.5 hours, the Zn/Cu-couple was filtered off, the solvent was evaporated under reduced pressure, and the residue was taken up in ethyl acetate (300 mL). The solution was washed with a 5% EDTA tri-sodium salt solution (2 x 50 mL), the aqueous phase was extracted with ethyl acetate (100 mL) and the combined organic layers were washed with water (100 mL) and brine (50 mL). After drying over sodium sulfate the solvent was evaporated under reduced pressure, the residue was dissolved in methanol (100 mL), and sodium methoxide (0.5 g) was added to a pH of 10. After stirring for two hours TLC indicated complete disappearance of starting material and Amberlite H^+ resin was added to neutralize the medium. The resin was filtered off, and the solvent was evaporated under diminished pressure. The residue was chromatographed on a silica gel column with dichloromethane/5% methanol as eluant. Removal of solvent in vacuo from fractions containing 10, followed by recrystallization from ethyl acetate gave 3.9 g (86%) of 10, m.p. 120-121°. IR (nujol): 3460; 3300-3000(br); 2950; 2840; 1645; 1570; 1450; 1360; 1280; 1070; 1030 cm^{-1}.

^{1}H NMR: (DMSO d_6) δ 8.2 (d, 1, C_5H, ^{5}(5-1') = 0.4 Hz); 7.7 and 7.6 (each bs, 1 each, NH, slight exchange with D_2O); 6.17 and 6.13 [(AB of ABXY, 2, H-3' and H-2' respectively;[a] J(2',3') = 6.1 Hz, J(2', 1') = 1.8 Hz, J(2',4') = 2.1 Hz,

J(3',4') = 1.4 Hz, J(3',1') = 2.3 Hz]; 6.02 (dddd, 1, H-1', J = 0.4, 1.6, 2.1, 3.8 Hz; 4.93 (t, 1, 5'-OH, exchanged with D_2O, J = 5.6 Hz); 4.92 (dddt, 1, H-4', J = 1.5, 2.3, 3.8, 5.4 Hz, couplings to H-3', H-2', H-1' and H-5'a,b respectively); 3.59 and 3.53, (AB of ABXY, 2, H-5'a,b; J(gem) = 11.2 Hz, J(5'-4') = 5.4, 5.4 Hz, J(5'-OH) = 5.7, 5.4 Hz.

^{13}C-NMR: (DMSO d_6) δ 173.1 (Stdd, C-2, J = 1.7, 5.2, 7.2 Hz)[a2]; 162.3 (Sd, C-4, $^2J_{CH}$ = 1.7 Hz); 150.2 (Sdd, C=O, J = 4.5, 6.8 Hz); 130.3 (Dsextets, [b3]C-2', J = 171.6, 3.6 Hz); 128.6 (Dq, [b]C-3', J = 175.0, 4.2 Hz); 124.7 (D, C-5, $^1J_{CH}$ = 192.7 Hz); 88.5 (Dtq, C-4', J = 148.3, 10.0, 2.4 Hz); 84.5 (Dt, C-1', J = 153.8, 10.7 Hz); 64.4 (Tdd, C-5', J = 141, ca. 3, ca. 7 Hz); [a] Two $^3J_{CH}$ to H-5, H-2'; 1.7 Hz coupling to H-1' or H-3'.

TLC: R_f 0.7. Anal. Calcd. for $C_9H_{10}N_2O_3S$: C, 47.77; H, 4.45; N, 12.38; S, 14.17. Found: C, 47.80; H, 4.62; N, 13.13; S, 13.94.

2-(2,3-Dideoxy-ß-D-glycero-pentofuranosyl)thiazole-4-carboxamide (11) (2',3'-dideoxytiazofurin): Tiazofurin-2'-ene (2.5 g, 10 mmol) was dissolved in methanol (100 mL), and maintained under a nitrogen atmosphere. Carefully 5% ethanol-pretreated palladium on barium carbonate (1 g) was introduced, and the hydrogenation was carried out at room temperature and atmospheric pressure during a two hour period. The catalyst was filtered off, the solvent was evaporated under reduced pressure and the residue was recrystallized from ethyl acetate; yield 2.1 g (84%); m.p. 94-95°. Analysis showed that the compound crystallized with 0.5 mol of water. IR (KBr): 3400-3050; 1670; 1380; 1190; 1050; 940 cm^{-1}.

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[2]Definitive assignment from ^{13}C spectrum based on hmbc present for H-5'a,b: δ 6.17, but not for δ 6.13.

[3]Assigned from hmbc.

^{1}H NMR: (DMSO d_6) δ 8.81 (s, 1, C_5H); 7.79 and 7.59 (each bs, 1 each, NH, partially exchanged with D_2O); 5.20 (dd, 1, H-1', J(1'-2'a,b) = 5.4, 7.9 Hz)[a4]; 4.88 (t, 1, 5'-OH, partially exchanged with D_2O, J = 5.5 Hz); 4.08 (tdd, 1, H-4', J(4'-5'a,b) = 5.3 Hz, J(4'-3'a,b) = 6.1, 7.5 Hz); 3.54 and 3.49[a] (each dd, 1 each, H-5'a,b, J(5'a,b-4') = 5.4, 5.2 Hz, J(gem) = 11.3 Hz); 2.41 (cm, 1, H-2'a); 2.03 (cm, 2, H-2'b, H-3'b); 1.71 (cm, 1, H-3'a).

[a5]Irradiation of H-4' produced no change in the absorption of H-1', indicating the absence of H(1'-4') coupling through the ribosyl oxygen or through C_2-C_3. The latter was observed when C_2-C_3 was unsaturated. Irradiation of H-4' gave rise to an AB pattern for H-5'a,b.

^{13}C-NMR: (DMSO d_6) 175.30 (Std, C-2, J = 4.5, 7.2 Hz); 162.80 (S, C-4); 150.15 (Sddd, C=O, J = 0.8, 4.9, 6.8 Hz[b6]); 124.38 (D, C-5, J_{CH} = 192.3 Hz); 81.73 (Dcm, C-4', J = 147.4, 8.2 Hz); 78.12 (Dcm, C-1', J = 151.8, 7.3 Hz); 63.93 (Tdd, C-5', J = 139.6, 2.0, 4.5 Hz); 33.09 (Tcm, C-3', J = 133.4 Hz); 27.71 (Tcm, C-2', J = 129.2 Hz);

TLC: Rf 0.70. Anal. Calcd. for $C_9H_{12}N_2O_3S$.: C, 47.35; H, 5.30; N, 12.27; S, 14.04. Found: C, 47.16; H, 5.41; N, 12.13; S, 13.78.

2-(5-Hydroxymethylfuran-2'-yl)thiazole-4-carboxamide (12):

Tiazofurin (8) (2.6 g, 10 mmol) was suspended in acetonitrile (30 mL) containing water (0.18 mL, 10 mmol) and α-acetoxyisobutyryl bromide (2) (4.5 mL, 30 mmol) is added in one portion. The reaction mixture was stirred for two hours when it formed a clear solution. Ethyl acetate (200 mL) was added, and the solution was washed with 5% sodium bicarbonate solution (2 x 50 mL), the aqueous phase was extracted with ethyl acetate (100 mL x 2), and the combined organic extracts were washed with water (50 mL) and brine (50 mL). After drying over

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[4]In a D_2O-exchanged sample, J=0.9; 4.6 Hz.

[5]Definitive assignment from ^{13}C spectrum based on hmbc present for H-5'a,b: δ 6.17, but not for δ 6.13.

[6]In a D_2O-exchanged sample, J=0.9; 4.6 Hz.

sodium sulfate the solvent was evaporated to yield a crude reaction product mixture (9).

The crude product was dissolved in anhydrous methanol (100 mL) and sodium methoxide (1.5 g) was added to adjust the pH value to 10. After stirring for two hours at room temperature the reaction mixture was neutralized with Amberlite resin H^+ (20 g). The resin was collected by filtration, the solvent was evaporated and the residue was recrystallized from methanol (25 mL) to yield 1.9 g (85%) of pure product, m.p. 192-194°; (lit. 192-193°). IR (KBr): 3420; 3380-3050(br); 1680; 1550; 1380; 1295; 1070; 1020; 890; 810 cm^{-1}.

^{1}H NMR: (DMSO d_6) δ 200 MHz 8.25 (s, 1, C_5H); 7.75 and 7.66 (each bs, 1 each, exchangeable with D_2O, NH); 7.11 (d, 1, ^{a}H-2', J(2'-3') = 3.4 Hz); 6.55 (d, 1, ^{a}H-3', J(3'-2') = 3.4 Hz); 5.45 (t, 1, 5'-OH, exchangeable with D_2O, J = 5.6 Hz); 4.50 (d, 2, H-5'a,b, J= 5.35 Hz); [a7]

^{13}C-NMR: (DMSO d_6) δ (Coupled with D_2O exchange); 162.35 (Sd, C-4, ^{2}JCCH = 1.4 Hz); 157.8 (Scm,[b8] C-4'); 157.2 (Sd, C-1', ^{2}JCCH = 7.7 Hz); 151.0 (Sdd, C=O, ^{3}JCCCH = 4.6 Hz, ^{2}JCNH = 7.2 Hz); 147.0 (Sdd, C-2'[b] ^{3}JCSCJ = ^{3}JCCCH = 8.4 Hz); 123.5 (Ds, C-5'[b] $^1J_{ch}$ = 194.7 Hz[c])[9]; 110.8 (Dd, C-2', J = 178.3, 4.6 Hz); 109.8 (Ddt, C-3', J = 177.3, 2.8, 3.8 Hz); 55.7 (Td, C-5', J - 142.8, 2.9 Hz).

TLC: Rf 0.55. Anal. Calcd. for $C_9H_8N_2O_3S$: C, 48.20; H, 3.60; N, 12.50; S, 14.30. Found: C, 48.38; H, 3.72; N, 12.49; S, 14.16.

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[7]Tentatively assigned. Similar chemical shifts and couplings were reported by Srivastava, et al[5]

[8]Most highly coupled carbon.

[9]The carbon chemical shifted and assignments for the thiazole ring for compounds **10-12** (Scheme 2) agree generally with those of Kovacs, et al. (23). The sole exception was C-2 of **12** which was shifted upfield to 147 ppm from its usual absorption at 172-3 ppm by the direct bonding to the furanosyl ring.

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